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Title: Efficacy of individualized homeopathic treatment of insomnia: Double-blind, randomized, placebo-controlled clinical trial

Author: Michael James

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Title: Efficacy of individualized homeopathic treatment of insomnia: Double-blind, randomized, placebo-controlled clinical trial

Running title: Homeopathic treatment of insomnia

Highlights

- We evaluated whether individualized homeopathy (IH) could produce significant effect beyond placebo in treatment of insomnia.
- In this double-blind, randomized, placebo-controlled, two parallel arms trial, 60 patients were randomized in 1:1 ratio to receive either IH or placebo.
- Patient-administered sleep diary (6 items) and Insomnia Severity Index (ISI) were taken as the primary and secondary outcomes respectively, measured at baseline, and after 3 months.
- Group differences were significant for sleep diary items 4, 5 and 6 ($P < 0.01$) and just significant ($P = 0.014$) for ISI score with moderate to large effect sizes; but non-significant for rest of the outcomes.
- IH seemed to produce significantly better effect than placebo in treatment of insomnia.

ABSTRACT

Background: Insomnia is the most common sleep-related complaint associated with impaired day-time functioning, reduced quality of life, increased morbidity and substantial societal cost. We evaluated whether individualized homeopathy (IH) could produce significant effect beyond placebo in treatment of insomnia.

Methods: In this double-blind, randomized, placebo-controlled, two parallel arms trial, 60 patients were randomized to receive either IH/verum or control/placebo (1:1). Patient-administered sleep diary (6 items; 1: latency to fall asleep, 2: minutes awake in middle of night, 3: minutes awake too early, 4: hours spent in bed, 5: total sleep time in hours, and 6: sleep

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efficiency) and Insomnia Severity Index (ISI) were taken as the primary and secondary outcomes respectively, measured at baseline, and after 3 months.

Results: Five patients dropped out (verum: 2, control: 3). Intention to treat sample (n=60) was analyzed. Trial arms were comparable at baseline. In the verum group, except sleep diary item 3 ($P = 0.371$), rest of the outcomes improved significantly (all $P < 0.01$). In the control group, there were significant improvements in diary item 6 and ISI score ($P < 0.01$) and just significant improvement in item 5 ($P = 0.018$). Group differences were significant for items 4, 5 and 6 ($P < 0.01$) and just significant ($P = 0.014$) for ISI score with moderate to large effect sizes; but non-significant ($P > 0.01$) for rest of the outcomes.

Conclusion: IH seemed to produce significantly better effect than placebo. Rigorous trials and independent replications are warranted. [Trial registration: CTRI/2017/05/008450; UTN: U1111-1195-7691]

ABBREVIATIONS

CI: Confidence Interval; CTRI: Clinical Trials Registry – India; IH: Individualized Homeopathy; ISI: Insomnia Severity Index; ITT: Intention to Treat; NIH: National Institute of Homoeopathy; RCT: Randomized Controlled Trials; SD: Standard Deviation; UTN: Universal Trial Number

KEYWORDS

Efficacy; homeopathy; insomnia; sleep diary; clinical trial

INTRODUCTION

Insomnia is a very common sleep disorder and is defined as the difficulty in initiating sleep or maintaining sleep, sleep difficulty at least 3 nights a week, or sleep difficulty that causes impairment of daytime functioning [1]. A number of factors can cause or contribute to insomnia, ranging from psychological disorders, over-the-counter medications to end-stage conditions such as Acquired Immunodeficiency Syndrome (AIDS), heart diseases, obstructive airway diseases, and renal diseases [1]. Besides, aging [2], genetics [3] and traumatic brain injuries [4] too have been found to contribute significantly to sleep quality. Conversely, insomnia can also be considered as a contributing factor to a multitude of diseases such as diabetes [5], hypertension [6], fibromyalgia [7], coronary heart disease [8] and an increased risk of mental disorders [9]. It is a significant risk factor especially for the development of depression [10, 11] and anxiety [12]. However, even when

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there are no symptoms of psychological disorders, a degree of disability in the performance of daily activities and social roles do occur in persons with sleep disorders [13]. Insomnia is the most common sleep-related complaint with a prevalence of 6-18% in the general population [14]. It is associated with impaired day-time functioning, reduced quality of life, increased risk of morbidity and substantial societal cost [15-17]. Numerous pharmacological and non-pharmacological therapeutic interventions (such as cognitive behavioral therapy) exist for the treatment of insomnia [18, 19]. However, the cycle of drug dependent insomnia can also result from commonly prescribed pharmacological agents even when used intermittently [20]. These treatments are not always fully effective and some have marked adverse effects. For these reasons, many patients suffering from insomnia try alternative therapies such as homeopathy [21]. There are a number of placebo controlled trials supporting the efficacy of homeopathic medicines in insomnia [22-24].

The outpatient department of National Institute of Homoeopathy (NIH) is often consulted by many patients suffering from sleep disorders. Hence, it provided a promising setting to conduct an efficacy trial of IH in insomnia. A systematic review of randomized trials of homeopathy for insomnia and sleep related disorders recommended that the future trials of homeopathy for insomnia should be conducted using adequate and rigorous designs [25]. It also pointed out the lack of intention to treat (ITT) analysis as a common shortcoming on the part of RCTs selected for review. Hence, the present work sought to assess the efficacy of IH in the patients suffering from insomnia and included ITT analysis.

We hypothesized that there might (alternative; Ha) or might not be (null; H_0) any significant difference between the groups receiving IH and placebo in the treatment of insomnia. We aimed to evaluate the efficacy of IH treatment against placebo in treatment of insomnia by detecting group differences, if any. We also intended to shortlist the most frequently indicated homeopathic medicines in insomnia.

METHODS

Trial design: This double-blind, randomized, prospective, placebo controlled, two parallel arms clinical trial was conducted at the out-patient departments of National Institute of Homoeopathy (NIH). The study protocol was approved by the Institutional Ethical Committee (IEC) [Ref. No. 5-023/NIH/PG/Ethical Comm. 2009/Vol. III/ 1957 (A/S); dated March 27, 2017] and was

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registered prospectively in the Clinical Trials Registry – India [CTRI/2017/05/008450] and had a secondary identifier – UTN of U1111-1195-7691. The trial protocol (unpublished) and full dissertation was submitted as the postgraduate thesis of the corresponding author to the West Bengal University of Health Sciences, Kolkata.

Participants: Inclusion criteria were the cases suffering from chronic insomnia [26] (ICD F51, G 47.0), both male and female patients, age between 18 and 65 years, and patients giving written consent to participate in the study. Exclusion criteria were those cases suffering from uncontrolled systemic illness or life-threatening infections, cases already undergoing homeopathic treatment for any chronic disease, substance abuse and/or dependence, pregnant or lactating women, patients with psychiatric diseases and self-reported immune-compromised states.

Intervention: Intervention was planned as administration of indicated homeopathic medicines in centesimal or 50 millesimal potencies and in individualized dosage, as decided appropriate to the case or condition. In centesimal potencies, each dose consisted of 4 cane sugar globules no. 30, moistened with a single drop of the indicated medicine, preserved in 90% v/v ethanol; repetition depending upon the individual requirement of the case and as per homeopathic principles. In 50 millesimal scale, a single medicated cane sugar globule of poppy seed size (no. 10) was dissolved in 90 ml of distilled water with addition of 2 drops of 90% v/v ethanol; 16 doses to be marked on the vial; each dose of 5 ml to be taken after 10 uniformly forceful downward strokes to the vial in 45 ml normal water in a clean cup, to stir well, to take 5 ml of this liquid orally, and to discard rest of the liquid from the cup. Each dose was directed to be taken orally on clean tongue with empty stomach. Duration of such therapy was 3 months. Medicines were obtained from SBL Pvt. Ltd. and Homoeopathy International® - Good Manufacturing Practice certified firms. Single individualized medicine was prescribed on each occasion taking into account presenting symptom totality, clinical history details, constitutional features, miasmatic expressions, repertorization using RADAR® software when required with due consultation with Materia Medica, and consensus among three homeopaths. Dose was also individualized and was based on homeopaths' judgment of susceptibility and consensus of three homeopaths. Subsequent prescriptions were generated as per Kent's observations and Hering's law. One of the prescribers possessed doctoral degree in homeopathy with more than 20 years of experience

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of practicing classical homeopathy and the rest were postgraduate trainees at NIH with minimum 3 years of experience. All the homeopaths involved were affiliated with respective state councils.

Control: Each dose in centesimal scale consisted of 4 cane sugar globules no. 30, moistened with a single drop of rectified spirit; identical in appearance with and indistinguishable from the medicine. In 50 millesimal scale, a single non-medicated cane sugar globule of poppy seed size (no. 10) was dissolved in 90 ml of distilled water with addition of 2 drops of 90% v/v ethanol; 16 doses to be marked on the vial; each dose of 5 ml to be taken after 10 uniformly forceful downward strokes to the vial in 45 ml normal water in a clean cup, to stir well, to take 5 ml of this liquid orally, and to discard rest of the liquid from the cup. Each dose was directed to be taken orally on clean tongue with empty stomach. Dosage and instructions were same as in the intervention arm. Duration of therapy was 3 months. Participants in the control arm were assessed similarly by the three homeopaths as was done in the experimental arm. 'Placebo prescription' was similar to that for patients receiving an actual medicine and could be identified only by the pharmacist as per the randomization chart. However, irrespective of codes, we planned to prescribe different 'acute medicines' (rescue remedies) based on 'acute totality' [27] to encounter any adverse or serious adverse events as per homeopathic principles.

General management: All the participants were encouraged to develop good sleep hygiene and habits such as not using bed for anything except sleep, maintaining regular sleep timings, avoiding behaviors such as napping after 3:00 pm, caffeine after lunchtime etc. which may interfere with sleep physiology. Patients were advised to be present for monthly follow-ups.

Outcomes:

- Primary – Sleep diary: It is a daily written record of an individual's sleep-wake pattern containing such information as time of retiring and arising, time in bed, estimated total sleep period, number and duration of sleep interruptions, quality of sleep [28]. The format used in this study had been used by Bakea (2003) as a subjective measurement against polysomnograph readings [29]. An advantage of sleep diaries was their prospective nature, which was less subject to bias (e.g., primacy, recency effects). They also yielded a series of quantitative values that could more precisely describe an individual's sleep patterns and could be useful in delivering behavioral treatments or measuring treatment-related changes

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[28]. In the present study, the data from the sleep diary were imported into a Master Sleep Diary Calculator (MSDC) developed by the Centre for Deployment Psychology, USA [30] to obtain the values of 6 items, namely, 'Latency to fall asleep' [item 1], 'Minutes awake in the middle of the night' [item 2], 'Minutes awake too early' [item 3], 'Hours spent in Bed' [item 4], 'Total Sleep Time in hours' [item 5] and 'Sleep Efficiency' [item 6]. For each patient, the 'Bed time' and 'Lights out' components of the MSDC were kept as the same; this change was adopted since in the population being studied, every patient allowed himself to sleep ('Lights out') almost at the same time as he went to bed ('Bed time') and the difference between the two terms were not well appreciated by the patients.

- Secondary – Insomnia Severity Index (ISI): Also known as Sleep Impairment Index (SII), the ISI was a 7- items measurement tool that yields a quantitative index of sleep impairment. It was a brief and global self-report instrument that provided valuable information on the patient's perception of his or her insomnia, its severity, level of distress and impairment of daytime functioning [31]. The ISI had been found to be sensitive to changes in insomnia research. It was a reliable and valid measure for the assessment of insomnia severity in a clinical population. It was a cost-efficient method to quantify perceived insomnia severity and might be used either as a screening device or as a measure of treatment outcome [32].

Sample size: Formal effect size and sample size calculation was not possible on account of underreporting of results of earlier trials of similar design. Assuming alpha error = 0.05, power 80%, and allocation ratio 1:1, and in order to detect a medium effect size (Cohen's d) of 0.5 by a two-tailed unpaired *t* test comparing difference between two independent means of sleep efficiency scores (sleep diary item 6; one of the specified primary outcomes) of two groups, sample size comes to 128 (i.e. 64 in each arm). However, keeping in mind the exploratory nature of the trial, stipulated time frame of 1 year and feasibility issue, restricting target sample size to 60 patients (i.e. 30 in each arm) seemed to be achievable. Given β/α ratio of 4, effect size of 0.5 and sample size of 30 in each arm, *post hoc* power analysis revealed a power compromise up to 60.4%.

Randomization: Intervention (IH) or comparator (placebo) was allocated per randomization chart generated by using the StatTrek random number generator. The chart was generated using

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restricted 6 blocks of size 10 (6 × 10 = 60) to maintain equal distribution between groups and 1:1 ratio easily; thus equal numbers of patients were randomized to code 1 or code 2 (either of verum/IH or control/placebo)

Blinding: The treating homeopaths, who were also the outcome assessors and the patients, were kept unaware (blinded/masked) of the generated allocation codes all through the study. Confidentiality of random-number generation and code allocation was maintained strictly and the people involved were not allowed to influence the study in any ways. The randomization chart was available confidentially only with the pharmacist, who was responsible for dispensing of either placebo or medicine, identical in appearance, to the patients according to the chart. Unblinding or breaking of the codes was done after the study had been completed and the database was frozen.

Statistical methods: The statistical analysis followed the intention-to-treat (ITT) approach; i.e. every included patient entered the final analysis. Missing values were replaced with regression means, last observation carried forward and multiple imputations using linear regression model. Baseline descriptive data (categorical and continuous) were presented in terms of absolute values, percentages, mean, standard deviations (sd), confidence intervals (CI), etc. Baseline differences were examined using unpaired *t* test for continuous data or chi-squared (χ^2) or Fisher's exact test (with Yates' correction) for categorical data. Group differences (for ISI scores and sleep diary derived items) at baseline (to check comparability) and over 3 months (to check efficacy) were tested by unpaired *t* test. Using paired *t* test, dependent observations of continuous outcomes over 3 months were also tested. *P* values less than 0.01 were considered as statistically significant. No interim and subgroup analyses were planned. SPSS®-IBM® v.20 for Windows was used for analysis of data. Reporting adhered to the CONSORT [33] and RedHot [34] guidelines for reporting trials, Mathie's criteria for model validity of homeopathic treatment [35, 36] (MVHT) and Saha's criteria for reporting quality of homeopathic individualization in clinical trials [37].

RESULTS

Participant flow: As per the pre-specified inclusion and exclusion criteria, 174 patients suffering from insomnia were screened; 114 were excluded on account of various reasons; 60 met the eligibility criteria and were enrolled into the trial. Following that, baseline socio-

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demographic and outcome data was obtained and were randomized to either IH (verum) or placebo (control). After 3 months of intervention, outcome data was recorded again. During course of treatment, 5 dropped out (2 in verum and 3 in control); 55 completed the trial. (Fig. 1)

Recruitment: Starting from May 2017, follow up of the last enrolled patient was completed by the end of June 2018.

Baseline data: Thirteen variables were studied across the two treatment groups – age, age groups, sex, residence, duration of suffering, food habit, risk factors, treatment taken, body mass index (BMI), marital status, education, employment status, and family income status to check whether the distribution of the variables between the two groups was statistically different or not, by using unpaired t-test and Chi-square/Fisher's exact test for continuous and categorical variables respectively. There was no significant difference in distribution of any of the variables between the two groups (all $P > 0.01$). (Table 1)

Numbers analyzed: Outcomes from 28/30 and 27/30 patients from the verum and placebo groups were complete respectively. However, as we planned to run ITT analysis, missing values were calculated.

Outcomes and estimation:

- Distribution at baseline: Distribution of the baseline outcome measures was similar between the two groups with no significant difference (all $P > 0.01$). However, sleep diary item 4, i.e. "hours spent in bed" was significantly higher in the control group than verum ($P = 0.002$); however, this difference might be caused by mere chance. Overall, it seemed that the groups were similar and comparable at baseline. (Table 2)
- Intra-group changes over 3 months: In the verum group, pair-wise analysis using paired *t*-test comparing baseline and after 3 months values showed significant improvement of ISI score ($P < 0.001$) and 5 out of 6 items of sleep diary (all $P < 0.01$, except item 3, $P = 0.371$). In the control group, similar analysis showed significant improvement of ISI score ($P < 0.001$) and item 6 of the sleep diary (item 6, $P<0.01$). All the other items of sleep diary showed no significant improvement. (Table 3)

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- Group differences over 3 months: The group differences in ISI score was just significant at $P = 0.014$ (medium effect size: Cohen's $d = 0.663$) and significant for items 4, 5 and 6 of the sleep diary (all $P < 0.001$, large effect size: Cohen's d for items 4, 5 and 6 were 0.955, 1.118 and 1.214 respectively). Sleep diary items 1, 2 and 3 showed no significant difference between groups (all $P > 0.01$). (Table 4)

Medicines used: The most frequently used medicines were *Natrum muriaticum* (n=10; 43.5%), *Nux vomica* (n=6, 26.1%), *Calcarea carbonicum*, *Lycopodium clavatum*, *Mercurius solubilis*, *Phosphorus*, and *Sulphur* (n=4 each; 17.4%), *Pulsatilla pratensis*, *Sepia succus*, and *Thuja occidentalis* (n=3 each; 13.0%). Though we kept provision for use of both centesimal and 50 millesimal potencies in the protocol, only the latter seemed to be appropriate and was used in the trial.

Adverse events: No harms, unintended effects, homeopathic aggravations or any serious adverse events were reported from either group. One adverse event of bleeding per rectum had occurred in a patient. To deal with, irrespective of the allocated code, *Phosphorus* 0/1 and 0/2 – 16 doses of each was prescribed in succession and that was sufficient to manage the condition.

DISCUSSION

Principal findings: This double blind, placebo-controlled, prospective, randomized, two parallel arms trial was carried out at National Institute of Homoeopathy on 60 patients suffering from insomnia and were treated with either individualized homeopathic medicines (n=30) or identical placebo (n=30). Sleep Diary and ISI were taken as primary and secondary outcome measures respectively, measured at baseline and after 3 months. Five patients had dropped out (verum: 2, control: 3). Intention to treat (ITT) sample (n=60) was analyzed. Trial arms were comparable at baseline. In the verum, except for sleep diary item 3 (minutes awake too early; $P = 0.371$), rest of the outcomes improved significantly (all $P < 0.01$). In the control group, there were significant improvements in sleep diary item 6 (sleep efficiency) and ISI score ($P < 0.01$) and just significant improvement in item 5 (total sleep time; $P = 0.018$). Group differences were

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significant for items 4 (hours spent in bed), 5 (total sleep time) and 6 (sleep efficiency); all $P < 0.01$ and just significant ($P = 0.014$) for ISI score with moderate to large effect sizes. Group differences were non-significant ($P > 0.01$) for rest of the outcomes (i.e. latency to fall asleep, minutes awake in middle of night and minutes awake too early). Individualized homeopathy seemed to produce significantly better effect than placebo.

Strengths of the study: It was a double blind, placebo controlled randomized clinical trial. The study was transparent in terms of prospective declaration and registration of protocol, ethical conduct and reporting. Prior to enrolment, each patient was provided with a patient information sheet in local vernacular Bengali detailing the study aims and objectives, methods, risks and benefits of participating and confidentiality issues. Subsequent to which, written informed consent was obtained. Thus the study conformed to every possible ethical standard. Clearance was obtained from the IEC prior to initiation. Though the sample size of this study was inadequate, still was adequately powered to detect changes in the specified outcome measure over 3 months. All the collected data (hard form) were converted into an analyzable and reproducible master chart (soft copy) where all data were extracted systematically and underwent statistical analysis subsequently. Missing values were replaced by appropriate statistical techniques; thus all the enrolled patients entered into the final analysis. The basis of treatment was individualized homeopathic treatment based on totality of symptoms and homeopathic principles.

Weakness of the study: One of the major weaknesses of the trial was the small duration of 3 months only; however, being a placebo-controlled trial, otherwise it would have raised ethical concerns. Secondly, the study was underpowered on account of small sample size; however, further increase of sample size was not feasible in the stipulated timeline. Though pre-validated sleep diary and ISI were used and were translated into Bengali using standardized forward-backward translation method, the psychometric validity and reliability of these outcomes remained to be addressed. Since both the outcome measures in this study were subjective retrospective measures depending on patient reports, those are amenable to be influenced by the subjective biases of the patients. Besides, repeatedly measured outcomes would have given enhanced robustness of the analyses instead of pair-wise comparisons.

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Strength and weakness in relation to other studies: Although there have been a number of studies on the efficacy of homeopathic medicines in insomnia, most of the studies utilized either non-individualized treatment such as *Coffea cruda* [22, 23, 39-41], *Nux vomica* [22, 23, 39] etc. or complex medicines [24]. Only two studies were found where individualized homeopathic medicines were administered [29, 42]. Results in both studies were in favor of homeopathic treatment for insomnia. In the study by Naudé, 2009 [29], the sleep diary data revealed that verum treatment resulted in a significant increase in 'duration of sleep' throughout the study compared to placebo. A significant improvement in SII summary scores was also observed in this study which utilized individualized homeopathic approach. 'Total sleep time' was also found to be increased by homeopathic treatment with *Nux vomica* or *Coffea cruda* in a study by Bell et al [22] in 2011 utilizing polysomnography as outcome measure. However, no significant changes were observed in actigraphic and self-rated scales. The present study also found significant increase in 'total sleep time' (sleep diary derived item 5) in the verum group after 3 months of treatment and no significant improvement in control group in this regard, thus supporting the findings of Naudé et al and Bell IR regarding the 'duration of sleep'. However, in the present study, the group difference in ISI score was found to be just significant in favor of verum with significant improvements simultaneously occurring in both verum and control groups. Although one study by Harrison et al in 2013, employing homeopathic complex preparation in psycho-physiological onset insomnia, observed significant gradual improvement in pre-sleep arousal as well as sleep onset latency in 4 weeks period [24], no significant changes were observed in these parameters in the present study of 12 weeks duration. However, total sleep time and sleep efficiency had improved significantly in verum group when compared to control group in the present study. Almost all the studies found favorable outcomes from administering homeopathic drugs. There was found increased total sleep time [22], improved mood [23], and improved duration of sleep [41]. However, one systematic review [25] which analyzed 6 RCTs [29, 41-45] found methodological flaws in all of them. All analyzed studies were underpowered, none included an ITT analysis and all except one [29] were poorly reported according to the review. The present study followed individualized homeopathic approach and included ITT analysis.

Unanswered questions and future research: The authors emphasize cautious interpretation of the study results. Validity and reliability of the translated Bengali version of the outcome measures remained to be addressed formally in future studies. The data were also helpful in the

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planning of adequately powered RCTs of individualized homeopathic treatment of insomnia in future with larger sample size. Independent replications and multi-centric trials of sufficient methodological robustness were warranted. Having objective measures such as polysomnography or actigraphy along with subjective measures might provide much more insight regarding efficacy of homeopathic medicines in insomnia in future trials. Having used only 50 millesimal potencies in this trial, pragmatic trials comparing efficacy of centesimal and 50 millesimal potencies or homeopathy versus usual care might also be fruitful ventures. The rationale behind having the centesimal potency available was that some homeopathic medicines available in centesimal potencies were either not available in 50 millesimal scales or their mode of preparation in 50 millesimal scales was controversial. Adhering only to 50 millesimal scales might have led to exclusion of any patient requiring the particular medicine. Hence, provision for centesimal scale medicines was also kept in the protocol. Besides, in comparison with 50 millesimal potencies, the method of intake of medicine in centesimal potencies was more convenient. It had often been observed that the patients find it troublesome to follow the instructions given for using 50 millesimal potencies. Since administration of individualized homeopathic treatment requires tailoring the medicines and dosage according to individual needs, keeping both scales of potentization available for use was considered preferable. However, while prescribing, the 50 millesimal potencies were given preference over centesimal potencies keeping in mind the alleged superiority of the former as suggested in homeopathic literature. It is claimed to be easier to tackle adverse events arising due to homeopathic medicines when using the 50 millesimal potencies over centesimal ones. The 50 millesimal scale was the latest one suggested by Dr. Samuel Hahnemann and considered superior to the centesimal scale (footnote to §270, 6th edition of Organon of Medicine). Further decisions regarding choice of potency were made broadly by keeping in view factors such as availability of the indicated medicines and patient's understandings of instructions for taking the medicine. Although the provision for administering centesimal potency was kept in the protocol, the medicines in 50 millesimal scales seemed to be sufficient to address all the needs. No prescriptions were made in centesimal potencies to the participants; hence no attempt was made to compare results based on potencies.

Conducting a double blind trial in homeopathy is indeed a daunting task, however that is not implausible. Although the nosological diagnosis might be the same for the group of patients

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selected for a trial, the homeopathic remedy and even its dosage that would have the best possible beneficial effect could be different for each individual. Studies that assessed the efficacy of the same remedy, being prescribed to all the participants in a trial for a particular disease were inherently at contradiction with the homeopathic principles of individualization and might not provide a valid representation for efficacy of homeopathy. Hence, adherence to the basic tenets of individualized homeopathy is suggested for any future trials aiming to assess efficacy of homeopathy.

CONCLUSION

In this double-blind, randomized, prospective, placebo-controlled, two parallel arms clinical trial conducted on 60 patients suffering from insomnia, there was statistically significant difference measured in sleep efficiency, total sleep time, time in bed, and ISI score in favor of homeopathy over placebo with moderate to large effect sizes. Group differences were non-significant for rest of the outcomes (i.e. latency to fall asleep, minutes awake in middle of night and minutes awake too early). Individualized homeopathy seemed to produce significantly better effect than placebo. Independent replications and adequately powered trials with enhanced methodological rigor are warranted.

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Figure 1: Study flow diagram

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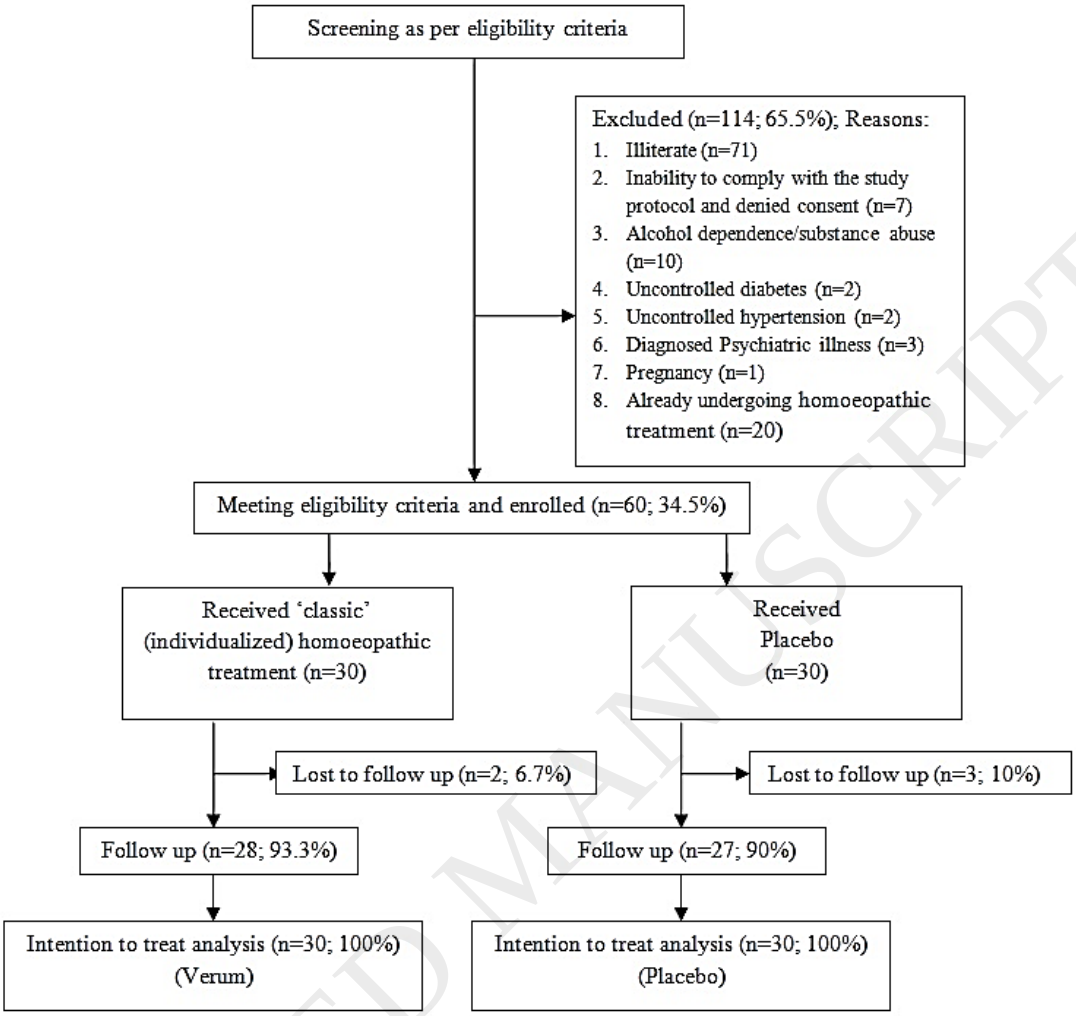

Table 1: Comparison of baseline features between two groups (N=60)

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Features	Homeopathy; n=30	Placebo; n=30	*P* values
Age[¥] (yrs; mean ± sd)	40.5 ± 11.3	37.4 ± 8.4	0.239
Age groups (yrs)[§]; n (%)			0.131
▪ 19 – 35	12 (40)	14 (47)	
▪ 36 – 50	12 (40)	15 (50)	
▪ 51 and above	6 (20)	1 (3)	
Sex[§]:			0.196
▪ Male	17 (57)	12 (40)	
▪ Female	13 (43)	18 (60)	
Residence[§]:			0.108
▪ Urban	8 (27)	14 (47)	
▪ Rural	22 (73)	16 (53)	
Duration of suffering[¥] (months; mean ± sd)	60.3 ± 65.8	72.0 ± 72.4	0.514
Food habit[§]:			0.554
▪ Vegetarian	2 (7)	1 (3)	
▪ Non-vegetarian	28 (93)	29 (97)	
Risk factor[§]:			0.739
▪ Tobacco	6 (20)	5 (17)	
Treatment taken[§]:			0.952
▪ None	3 (10)	3 (10)	
▪ Usual care	8 (27)	10 (34)	
▪ Homeopathy	18 (60)	16 (53)	
▪ Others	1 (3)	1 (3)	
BMI[§]:			0.826
▪ Underweight	6 (20)	5 (17)	
▪ Normal	21 (70)	23 (77)	
▪ Overweight	3 (10)	2 (6)	
Marital status[§]:			0.116
▪ Married	28 (93)	24 (80)	
▪ Single	2 (7)	2 (7)	
▪ Others	0 (0)	4 (13)	
Education[§]; n (%)			0.606
▪ 10^{th} std. or below	25 (83)	22 (73)	
▪ 11^{th} – 12^{th} std	3 (10)	4 (14)	
▪ Above 12^{th} std	2 (7)	4 (13)	
Employment status[§]:			0.056
▪ Self-employed	16 (53)	8 (27)	
▪ Service	2 (7)	7 (23)	
▪ Unemployed	12 (40)	15 (50)	
Family income status[§]:			0.094
▪ Poor	18 (60)	24 (80)	
▪ Middle	12 (40)	5 (17)	
▪ Affluent	0 (0)	1 (3)	

[§] Chi-squared/Fisher test; [¥] Independent *t* test; $P < 0.01$ considered as statistically significant

Table 2: Baseline comparison of the outcome scores (N=60)

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Outcome measures	Homeopathy; n=30	Control; n=30	*P* value [a]
ISI score	20.6 ± 3.4	20.1 ± 4.3	0.573
Sleep diary items			
▪ Item 1	65.8 ± 33.9	82.4 ± 72.6	0.261
▪ Item 2	123.1 ± 44.3	129.0 ± 53.1	0.642
▪ Item 3	57.4 ± 30.2	59.4 ± 31.8	0.803
▪ Item 4	6.6 ± 1.2	7.6 ± 1.1	0.002*
▪ Item 5	2.5 ± 1.3	3.1 ± 1.3	0.113
▪ Item 6	37.5 ± 17.8	39.7 ± 15.1	0.611

[a] Unpaired *t* test; $P < 0.01$ considered as statistically significant; *Significant differences

Table 3: Intra-group changes after 3 months of treatment (N=60)

Outcome measures	Baseline: mean ± sd	After 3 mo: mean ± sd	Changes: mean ± sd (95% CI)	*P* value [a]
Homeopathy (n=30):				
ISI score	20.6 ± 3.4	13.9 ± 4.6	6.7 ± 5.6 (4.6 to 8.8)	< 0.001*
Sleep diary items				
▪ Item 1	65.8 ± 33.9	55.2 ± 28.4	10.6 ± 13.6 (5.5 to 15.7)	< 0.001*
▪ Item 2	123.1 ± 44.3	107.2 ± 50.0	15.9 ± 26.7 (5.9 to 25.9)	0.003*
▪ Item 3	57.4 ± 30.2	53.9 ± 22.0	3.5 ± 21.2 (-4.4 to 11.5)	0.371
▪ Item 4	6.6 ± 1.2	7.0 ± 1.2	-0.4 ± 0.6 (-0.6 to -0.1)	0.002*
▪ Item 5	2.5 ± 1.3	3.4 ± 1.3	-0.9 ± 0.6 (-1.1 to -0.6)	< 0.001*
▪ Item 6	37.5 ± 17.8	48.2 ± 17.0	-10.8 ± 5.6 (-12.8 to -8.7)	< 0.001*
Placebo (n=30):				
ISI score	20.1 ± 4.3	16.6 ± 3.3	3.5 ± 4.1 (1.9 to 5.0)	< 0.001*
Sleep diary items				
▪ Item 1	82.4 ± 72.6	77.4 ± 57.6	5.0 ± 23.6 (-3.8 to 13.8)	0.258
▪ Item 2	129.0 ± 53.1	120.9 ± 50.6	8.1 ± 36.5 (-5.5 to 21.7)	0.235
▪ Item 3	59.4 ± 31.8	49.3 ± 42.5	10.2 ± 35.0 (-2.9 to 23.2)	0.122
▪ Item 4	7.6 ± 1.1	7.4 ± 1.2	0.2 ± 0.6 (-0.0 to 0.4)	0.105
▪ Item 5	3.1 ± 1.3	3.3 ± 1.3	-0.2 ± 0.5 (-0.4 to -0.0)	0.018
▪ Item 6	39.7 ± 15.1	43.6 ± 15.5	-3.9 ± 5.9 (-6.1 to -1.7)	0.001*

[a] Paired *t* test; $P < 0.01$ considered as statistically significant; *Significant differences

Table 4: Group differences after 3 months of treatment

Outcomes	Changes in IH group; mean ± sd	Changes in Placebo group; mean ± sd	Mean difference ± SE (95% CI)	*P* value [a]	Cohen's *d*
ISI score	6.7 ± 5.6	3.5 ± 4.1	3.2 ± 1.3 (0.7 to 5.7)	0.014	0.663
Sleep diary items					
▪ Item 1	10.6 ± 13.6	5.0 ± 23.6	5.7 ± 5.0 (-4.3 to 15.6)	0.260	0.299
▪ Item 2	15.9 ± 26.7	8.1 ± 36.5	7.8 ± 8.3 (-8.7 to 24.4)	0.347	0.249
▪ Item 3	3.5 ± 21.2	10.2 ± 35.0	-6.6 ± 7.5 (-21.6 to 8.3)	0.377	0.233
▪ Item 4	-0.4 ± 0.6	0.2 ± 0.6	-0.5 ± 0.1 (-0.8 to -0.2)	0.001*	0.955
▪ Item 5	-0.9 ± 0.6	-0.2 ± 0.5	-0.6 ± 0.1 (-0.9 to -0.3)	< 0.001*	1.118
▪ Item 6	-10.8 ± 5.6	-3.9 ± 5.9	-6.8 ± 1.5 (-9.8 to -3.9)	< 0.001*	1.214

[a] Unpaired *t* test, $P < 0.01$ considered as statistically significant; * significant differences